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Outcome After Normal Exercise Echocardiography and Predictors of Subsequent Cardiac Events: Follow-Up of 1,325 Patients

ROBERT B. McCULLY, MB, ChB, FACC, VERONIQUE L. ROGER, MD, FACC, DOUGLAS W. MAHONEY, MS, BARRY L. KARON, MD, FACC, JAE K. OH, MD, FACC, FLETCHER A. MILLER, Jr., MD, FACC, JAMES B. SEWARD, MD, FACC, PATRICIA A. PELLIKKA, MD, FACC

Rochester, Minnesota

Objectives. **This study sought to examine the outcome of a large group of patients after normal exercise echocardiography and to identify potential predictors of subsequent cardiac events.**

Background. **Earlier studies suggested that prognosis after normal exercise echocardiography is favorable, with a low subsequent cardiac event rate. These studies involved a small number of patients and did not have sufficient statistical power to stratify risk.**

Methods. **The outcomes of 1,325 patients who had normal exercise echocardiograms were examined. End points were overall and cardiac event-free survival. Cardiac events were defined as cardiac death, nonfatal myocardial infarction and coronary revascularization. Patient characteristics were analyzed in relation to time to first cardiac event in a univariate and multivariate manner to determine which, if any, were associated with an increased hazard of subsequent cardiac events.**

Results. **Overall survival of the study group was significantly better than that of an age- and gender-matched group obtained from life tables ($p < 0.0001$). The cardiac event-free survival rates at 1, 2 and 3 years were 99.2%, 97.8% and 97.4%, respectively. The cardiac event rate per person-year of follow-up was 0.9%. Subgroups with an intermediate or high pretest probability of having coronary artery disease also had low cardiac event rates. Multivariate predictors of subsequent cardiac events were angina during treadmill exercise testing (risk ratio [RR] 4.1, 95% confidence interval [CI] 1.5 to 11.0), low work load (defined as <7 metabolic equivalents [METs] for men and <5 METs for women; RR 3.2, 95% CI 1.4 to 7.6), echocardiographic left ventricular hypertrophy (RR 2.6, 95% CI 1.1 to 6.3) and advancing age (RR 1.04/year, 95% CI 1.0 to 1.1).**

Conclusions. **The outcome after normal exercise echocardiography is excellent. Subgroups with an intermediate or high pretest probability of having coronary artery disease also have a favorable prognosis after a normal exercise echocardiogram. Characteristics predictive of subsequent cardiac events (i.e., patient age, work load, angina during exercise testing and echocardiographic left ventricular hypertrophy) should be considered in the clinical interpretation of a normal exercise echocardiogram.**

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The clinical use of exercise echocardiography is expanding rapidly. When performed by experienced operators, the diagnostic accuracy of this cardiac stress-testing modality is similar to that reported with nuclear imaging techniques (1). Prognostic data pertaining to exercise echocardiography have been accumulating in different clinical contexts (2–8). Earlier small studies have suggested that a normal exercise echocardiogram portends a favorable prognosis (2,3). A normal exercise echocardiogram result, therefore, usually leads to physician reassurance of the patient.

The purposes of the present study were to examine the outcome of a large number of patients with normal exercise echocardiograms and to determine whether any clinical, exercise or echocardiographic variables are predictive of subsequent cardiac events.

Methods

Study group. All patients undergoing stress echocardiography from December 1989 to April 1994 were prospectively entered into a computer data base. This data base included 3,690 patients (mean age [±SD] 62 ± 13 years; 61% men) with a first-time exercise echocardiogram at the Mayo Clinic. Of these echocardiograms, 1,761 were interpreted as normal. Patients with a history of myocardial infarction, previous coronary revascularization, previous coronary arteriography, echocardiographic evidence of cardiomyopathy (dilated, hypertrophic or restrictive), significant valvular disease or ascending aortic aneurysm were excluded. On the basis of these criteria, 349 patients were excluded; thus, 1,412 patients formed the study group. There were no other clinical or

From the Division of Cardiovascular Diseases and Internal Medicine and Section of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was supported by the Mayo Foundation.

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Address for correspondence: Dr. Robert B. McCully, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905.

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Abbreviations and Acronyms
ECG = electrocardiogram, electrocardiographic
METs = metabolic equivalents
RR = risk ratio

technical exclusions. The pretest probability of coronary artery disease was determined using an algorithm based on previous studies (see Appendix) (9,10).

Exercise echocardiography protocol. Treadmill exercise testing was performed on all patients. The Bruce protocol was used most frequently (85%), but modified Bruce and Naughton protocols were also used if deemed necessary. Two-dimensional echocardiographic images at rest and immediately after exercise were acquired, digitized, recorded and analyzed according to a standardized, previously published protocol (1). Both digitized and videotape-recorded images were used for interpretation of the studies. Reviewers had no knowledge of clinical and exercise data. A normal exercise echocardiogram was defined as such by the presence of a normal or hyperdynamic response to exercise of all 16 left ventricular myocardial segments (11) judged to be normal at rest. Left ventricular wall thickness was measured by two-dimensional or M-mode echocardiographic measurements of the septum and posterior wall in the parasternal long-axis or short-axis view at the mid-ventricular level. Patients were defined as having left ventricular hypertrophy if the diastolic thickness of the septum or posterior wall was >13 mm.

Follow-up. Follow-up was obtained by mailed questionnaires, scripted telephone interviews and review of medical records. Ninety-eight percent of the patients were contacted. Contact was not possible for 30 patients (2%), 21 of whom lived outside the United States. Fifty-seven patients (4%) who were contacted declined to participate in the study. Therefore, complete follow-up was obtained for 1,325 patients (94%).

End points. The end points were noncardiac death and cardiac events (i.e., cardiac death [sudden or preceded by an ischemic cardiac syndrome], nonfatal myocardial infarction and coronary revascularization [coronary artery bypass graft surgery or angioplasty]). All cardiac events were verified by contacting the patients' primary physician and obtaining relevant medical records or death certificates.

Statistical analysis. Baseline clinical, exercise and echocardiographic characteristics of the study group were summarized as the mean value ± SD for continuous variables and as a percentage of the group total for discrete variables. These characteristics were compared between patient subgroups using the Wilcoxon rank-sum test and the chi-square test for continuous and categoric variables, respectively. Overall and cardiac event-free survival was estimated using the Kaplan-Meier method. Overall survival was compared with expected survival of an age- and gender-matched group (survival curves obtained from life tables of the white, west north central U.S. population). For the event-free survival analysis, the patients with noncardiac deaths were censored at the time of death but not included as cardiac events. The association of clinical, exercise and echocardiographic characteristics with time to first cardiac event was investigated within the Cox proportional hazards framework. A stepwise forward variable selection procedure was used to determine the final multivariate model from the 26 candidate predictor variables investigated. For the model-building process, the entry and retention criteria were set at an alpha level of 0.05. Based on the variables found to be independent predictors of subsequent cardiac events, a risk score was calculated for each patient. The dichotomized value of the risk score that resulted in the largest change in the partial likelihood function was used to classify patients as being at low risk or at increased risk for subsequent cardiac events.

Table 1. Clinical Characteristics of 1,325 Patients in the Study Group With Follow-Up

Characteristic	% of Patients
Women	52
Chest pain history	
None	39
Atypical chest pain	50
Typical angina	11
Hypertension	37
Diabetes mellitus	6
Smoking	44
Family history of CAD*	36
Hypercholesterolemia†	50
Medications	
Beta-blockers	15
Calcium channel blockers	18
Digoxin	7
Rest ECG	
Normal	59
Q waves	2
ST-T wave changes	35
LBBB	2
RBBB	3

*First-degree relative <65 years old. †Total cholesterol >200 mg/dl or lipid-lowering drug use. CAD = coronary artery disease; ECG = electrocardiogram; LBBB = left bundle branch block; RBBB = right bundle branch block.

Results

Baseline clinical characteristics. Exercise echocardiography was performed for evaluation of chest pain or dyspnea in 72% of the patients, as part of a preoperative evaluation in 3% and for other reasons in 25%. The mean age ±SD of the 1,325 patients who had follow-up was 57 ± 13 years. Their clinical characteristics are summarized in Table 1.

Exercise echocardiographic characteristics. The exercise echocardiographic characteristics of the patients who had follow-up are summarized in Table 2. The exercise electrocardiogram (ECG) was positive for myocardial ischemia (≥1 mm horizontal or downsloping ST segment depression at 80 ms after the J point in one or more leads) in 8% of women and 7% of men (p = NS).

Table 2. Exercise Echocardiographic Characteristics of 1,325 Patients With Follow-Up Data

Work load	
<5 METs	6%
<7 METs	26%
<10 METs	60%
<7 METs (men), <5 METs (women)	11%
<85% Age-predicted max HR achieved	17%
Maximal HR (beats/min)	155 ± 23
Maximal SBP (mm Hg)	180 ± 28
Maximal DBP (mm Hg)	87 ± 14
Rate–pressure product, peak	27,929 ± 6,120
Exercise hypertension (peak SBP >240 mm Hg)	9%
Exercise hypotension (peak SBP < rest SBP)	3%
Angina during TMET	5%
Exercise ECG positive for ischemia	8%
Echo EF, rest (%)	61 ± 5
Echo EF, peak (%)	71 ± 5
Echo LVH	11%
Image acquisition time (min)	1.4 ± 0.4

Data are presented as percentage of patients or mean value ± SD. DBP = diastolic blood pressure; Echo = echocardiographic; EF = ejection fraction; HR = heart rate; LVH = left ventricular hypertrophy; max = maximal; METs = metabolic equivalents; SBP = systolic blood pressure; TMET = treadmill exercise test.

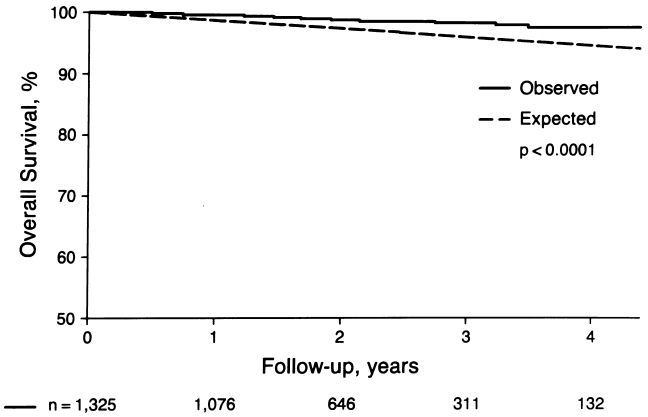

Figure 1. Overall survival curves of patients with follow-up (observed, n = 1,325) and an age- and gender-matched group obtained from life tables (expected). End points were noncardiac and cardiac deaths.

With regard to these baseline clinical and exercise echocardiographic characteristics, patients with follow-up were not significantly different from those without follow-up or those unwilling to participate in the study (n = 87; mean age 55 ± 14 years) except for a lower prevalence of echocardiographic left ventricular hypertrophy (11% vs. 18%, p = 0.026).

Clinical outcome. The median length of follow-up for the 1,325 patients was 23 months (range 5 to 65). There were 14 noncardiac deaths. The cause of death in these patients was cancer in seven, trauma in three, pulmonary embolism in two, alcoholic liver disease in one and pneumonia in one. There were 33 cardiac events in 26 patients. Three patients died of cardiac causes (fatal myocardial infarction in two and sudden cardiac death in one). These deaths occurred 14, 19 and 20 months after the exercise echocardiogram. Ten patients had nonfatal myocardial infarction and 20 underwent coronary revascularization. Overall survival of the study group was higher than expected survival of an age- and gender-matched group (p < 0.0001) (Fig. 1). Survival rates free of cardiac death or nonfatal myocardial infarction at 1, 2 and 3 years were 99.5 ± 0.2%, 98.8 ± 0.4% and 98.6 ± 0.4%, respectively. The cardiac death and nonfatal myocardial infarction rate per person-year of follow-up was 0.5%. Survival rates free of all cardiac events (cardiac death, nonfatal myocardial infarction or coronary revascularization) at 1, 2 and 3 years were 99.2 ± 0.3%, 97.8 ± 0.5% and 97.4 ± 0.6%, respectively. The cardiac event rate per person-year of follow-up was 0.9%.

Pretest probability of disease. The pretest probability of coronary artery disease was low (≤25%) in 55% of patients, intermediate (26% to 69%) in 35% and high (≥70%) in 10%. The cardiac death and nonfatal myocardial infarction rates per person-year of follow-up for the low, intermediate and high pretest probability subgroups were 0.4%, 0.6% and 0.8%, respectively (p = 0.54). The cardiac event rate per person-year of follow-up for these subgroups was 0.5%, 1.5% and 1.6%, respectively (p = 0.01).

Univariate predictors of cardiac events. Univariate predictors of time to cardiac event, risk ratios and p values are given in Table 3. Low work load was defined as achievement of <7 metabolic equivalents (METs) for men and <5 METs for women, because the expected treadmill time for men is, on average, 2 to 3 min longer than that for women (Bruce protocol) (12). The univariate Kaplan-Meier survival curves of patients with low versus good work load are shown in Figure 2. A history of typical angina and positive exercise ECG were not univariately predictive of subsequent cardiac events.

Multivariate predictors of cardiac events. The development of angina during treadmill exercise testing conferred a

Table 3. Univariate Predictors of Time to Cardiac Event

Variable*	RR (95% CI)	p Value
Low work load†	5.6 (2.6–12.5)	0.0001
Exercise hypotension	4.5 (1.3–15.3)	0.01
Angina during TMET	4.4 (1.6–11.6)	0.003
Echo LVH	4.1 (1.8–9.5)	0.001
Diabetes mellitus	3.8 (1.4–10.2)	0.007
<85% Age-predicted max HR achieved	2.4 (1.1–5.5)	0.03
Hypertension	2.4 (1.1–5.2)	0.03
Pretest probability	1.9 (1.1–3.1)	0.01
Age (per yr)	1.1 (1.03–1.1)	0.0005

*Other (nonsignificant) variables tested included gender; family history of coronary artery disease; hypercholesterolemia; smoking; history of typical angina; use of beta-blockers, calcium channel blockers or digoxin; abnormal rest electrocardiogram; exercise electrocardiogram positive for myocardial ischemia; maximal heart rate; maximal systolic blood pressure and diastolic blood pressure; peak exercise rate–pressure product; exercise hypertension; and rest and exercise echocardiographic ejection fraction. †Defined as <7 metabolic equivalents (METs) for men, <5 METs for women. CI = confidence interval; RR = risk ratio; other abbreviations as in Table 2.

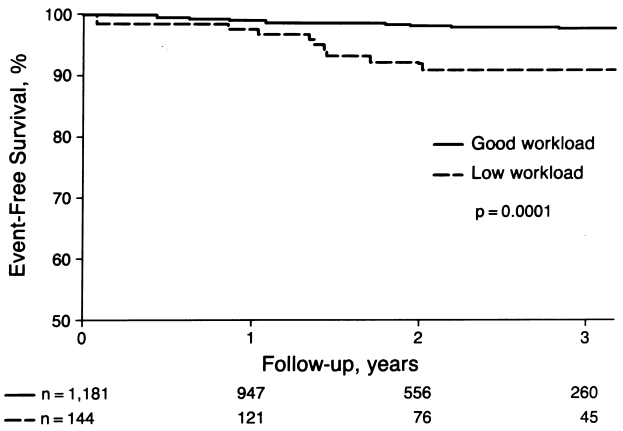

Figure 2. Event-free survival of patients with a low work load (<7 METs for men and <5 METs for women) and a good work load. The 1- and 2-year event-free survival rates for those with a low work load were 97.8 ± 1.2% and 91.1 ± 2.7%, respectively, and for those with a good work load, 99.4 ± 0.2% and 98.7 ± 0.4%, respectively.

risk ratio (RR) of 4.1 for subsequent cardiac events. Other multivariate predictors were a low work load (RR 3.2), echocardiographic left ventricular hypertrophy (RR 2.6) and advancing age (RR 1.04 per year). The results of the final multivariate model are summarized in Table 4.

Normal exercise echocardiographic score. The multivariate predictor variables, appropriately weighted according to their parameter estimates, were used to calculate a risk score for each patient: Risk score = (Age × 0.04) + (1.17 if the work load was low) + (0.97 if there was echocardiographic left ventricular hypertrophy) + (1.42 if there was angina during the treadmill exercise test). This multivariate risk score is summarized and displayed in Figure 3A. A low risk subset, consisting of patients with a score ≤4, had a cardiac event rate per person-year of follow-up of 0.6%. A higher risk subset comprised patients with a score >4; this subset had a cardiac event rate per person-year of follow-up of 4.8%. The event-free survival of these subsets is shown in Figure 3B.

Discussion

In this study of 1,325 patients whose coronary artery status was unknown, the prognosis after normal exercise echocardiography was excellent. The overall survival of the study group was better than that of an age- and gender-matched group selected from life tables (p = 0.0001). This was most likely due to the fact that the patients in the study group had normal left ventricular systolic function, no significant valvular disease and, for the most part, the capability of exercising (13). The cardiac event-free survival rates at 1, 2 and 3 years were 99.2%, 97.8% and 97.4%, respectively. The majority of patients were referred to the stress echocardiography laboratory for evaluation of symptoms that were possibly due to coronary artery disease. The pretest probability of coronary artery disease was low in 55% of patients and intermediate or high in 45%. Patients with an intermediate or high pretest probability also had a favorable prognosis. Pretest probability of disease, included as a variable in the outcome analysis, was not an independent predictor of subsequent cardiac events.

Table 4. Multivariate Predictors of Time to Cardiac Event

Variable	Parameter Estimate (SE)	RR (95% CI)	p Value
Angina during TMET	1.42 (0.50)	4.1 (1.5–11.0)	0.005
Low work load*	1.17 (0.43)	3.2 (1.4–7.6)	0.007
Echo LVH	0.97 (0.44)	2.6 (1.1–6.3)	0.03
Age (per yr)	0.04 (0.02)	1.04 (1.0–1.1)	0.03

*Defined as <7 metabolic equivalents (METs) for men, <5 METs for women. Other abbreviations as in Tables 2 and 3.

Predictors of clinical outcome. Independent predictors of subsequent cardiac events were low work load, development of angina during the treadmill exercise test, echocardiographic left ventricular hypertrophy and age. Low work load (<7 METs for men and <5 METs for women) was defined as such because the expected treadmill time is higher in men than in women (12). The diagnostic and prognostic power of all exercise stress-testing modalities depends on the work load achieved at the time of the test. Thus, several studies have shown that patients who can exercise into stage 4 of the Bruce protocol (>10 METs) have a favorable outcome, even if they have marked ST segment depression (14–16) or three-vessel coronary artery disease (17). The present study showed that, in the context of a normal exercise echocardiogram, men who can exercise into stage 3 and women who can exercise into stage 2 of the Bruce protocol have an excellent prognosis. Development of angina during the exercise test was also predictive of subsequent events, but neither a history of typical angina nor the development of a positive exercise ECG was predictive. The finding that echocardiographic left ventricular hypertrophy (as defined) was predictive of subsequent cardiac events was an incidental finding, but is consistent with previous studies showing that left ventricular hypertrophy has an adverse effect on prognosis in patients with and those without coronary artery disease (18–20). It is unlikely that left ventricular hypertrophy was a predictor of events simply because its presence affected the diagnostic accuracy of the exercise echocardiogram, resulting in false negative results. A recently published study showed that the sensitivity (and specificity) of exercise echocardiography was not affected by the presence of left ventricular hypertrophy (21). A higher prevalence of coronary artery disease is seen with advancing age (9), explaining why age was a predictor of subsequent events. A normal exercise echocardiographic risk score, based on the four independent predictors of outcome in this study, was used to identify a subset of patients at increased risk for subsequent cardiac events (Fig. 3, A and B); patients in this subset should be considered for further evaluation.

Previous studies. The prognostic value of a normal exercise echocardiogram has been investigated in two published studies with follow-up of a total of 263 patients (2,3). In the initial study, 170 patients underwent treadmill exercise testing

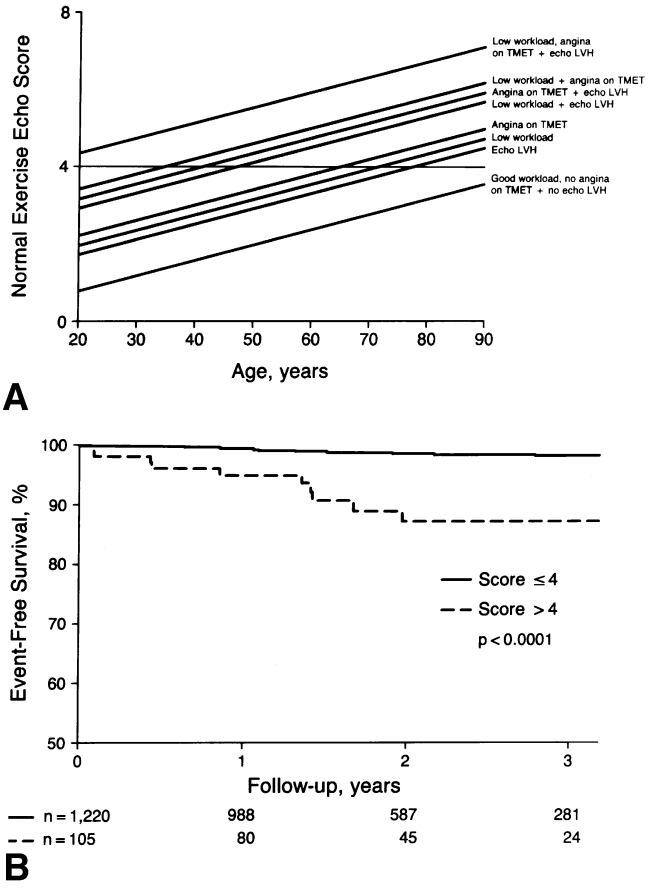

Figure 3. A, Diagram of normal exercise echocardiographic risk score according to age and number of predictor characteristics present. For example, if a 65-year old man exercised for 9 min (10 METs) of the Bruce protocol but developed angina on the treadmill exercise test and had echocardiographic left ventricular hypertrophy (LVH), he would have a score of 5 and be at increased risk for subsequent cardiac events. Echo = echocardiographic; TMET = treadmill exercise test. **B,** Event-free survival curves of patients with a normal exercise echocardiographic risk score ≤4 and those with a risk score >4. The 1- and 2-year event-free survival rates for those with a score ≤4 were 99.6 ± 0.2% and 98.7 ± 0.4%, respectively, and for those with a score >4, 95.0 ± 2.2% and 87.1 ± 4.0%, respectively.

with immediate postexercise echocardiographic imaging (2). Follow-up was 87% complete. The myocardial infarction rate was 0.85% per year and the coronary revascularization rate was 1.7% per year. There were no deaths during the follow-up period, which averaged 28 months. More recently, the outcome of 137 patients undergoing upright bicycle exercise testing with imaging at peak exercise was reported (3). Follow-up was 84% complete, and the mean follow-up period was 23 months. The cardiac event rate was 1.8% per year. Events included myocardial infarction and coronary revascularization. There were no deaths. These results are similar to those of the present study and studies on normal exercise thallium-201 myocardial perfusion scintigraphy (22).

Study limitations. The number of cardiac deaths and nonfatal myocardial infarctions during the relatively short follow-up period (median 23 months) was low. In the analysis of variables associated with subsequent cardiac events, coronary revascularization was included as a cardiac event. It was thought that although the decision to perform coronary revascularization is a subjective one, it does reflect a clinical event and is an appropriate end point to use for outcome analysis, particularly in patients with normal exercise echocardiograms. Including coronary revascularization permitted multivariate modeling of the data without excessive overfitting of the models.

The multivariate risk score was not tested in a different group of patients for the purpose of validation. However, as outlined in the Discussion, characteristics making up the risk score have been found to be of prognostic value in other studies (14,15,18–20,23).

The generalizability of these results to other practice settings may be debated because of the makeup of the study group and the reproducibility of exercise echocardiographic interpretation. The study group's average age was 57 years and it was part of a large population of patients examined at a large tertiary medical center. Most patients in the study group were symptomatic and 45% had an intermediate or high pretest probability of having coronary artery disease. Thus, the study group would seem representative of the population undergoing stress testing in laboratories where a large number of tests are performed. The data on interobserver variability in the interpretation of stress echocardiography are limited and somewhat conflicting (24,25). One study recently showed only fair interinstitutional agreement but reported higher agreement in patients with no coronary artery disease (25). In a study of normal stress echocardiograms, therefore, one should expect reasonably good reproducibility.

The diagnosis of left ventricular hypertrophy was not based on the calculation of left ventricular mass but on the measurement of ventricular septal or posterior wall thickness. The calculation of left ventricular mass may have provided different information and results. However, the various methods used for calculation of left ventricular mass have limitations (26,27).

Conclusions. This study confirms that the outcome after normal exercise echocardiography is excellent. Even patients with a clinically intermediate or high pretest probability of having coronary artery disease had a favorable prognosis after normal exercise echocardiography. However, within this overall low risk group of patients is a subset of patients at increased risk for subsequent cardiac events. This subset can be identified by making use of certain clinical, exercise and echocardiographic characteristics that are predictors of subsequent cardiac events. These patient characteristics should be considered in the clinical interpretation of a normal exercise echocardiogram.

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Appendix

Pretest Probability of Coronary Artery Disease

Estimation of pretest probability of coronary artery disease was based on previously published data. A history of chest pain was considered more important than the presence of risk factors. In the data base of our study group, no distinction was made between "atypical angina" and "nonanginal chest pain." Therefore, to determine which of our patients with "atypical chest pain" were in the low or intermediate pretest probability subgroups, we averaged the pretest probabilities of the "atypical angina" and "nonanginal chest pain" subgroups of Diamond and Forrester (9), according to gender and age. Low, intermediate and high pretest probability of disease was defined as a probability of ≤25%, 26% to 69% and ≥70%, respectively. The risk factors considered were those used by Patterson and Horowitz (10)—namely, hypertension, smoking, diabetes mellitus, hypercholesterolemia and ST-T segment wave changes (including those associated with left bundle branch block) on the rest ECG. Patients without a history of chest pain were stratified on the basis of gender, age and the number of risk factors present using these authors' graphs:

Low pretest probability (n = 726 [55%])
- No chest pain
  - All women
  - Men with <3 risk factors
  - Men with ≥3 risk factors if <50 years old
- Atypical chest pain
  - Women <60 years old
  - Men <40 years old

Intermediate pretest probability (n = 466 [35%])
- No chest pain
  - Men with ≥3 risk factors if ≥50 years old
- Atypical chest pain
  - Women ≥60 years old
  - Men ≥40 years old
- Typical angina
  - Women <50 years old
  - Men <30 years old

High pretest probability (n = 133 [10%])
- Typical angina
  - Women ≥50 years old
  - Men ≥30 years old

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